HAEMA (Αίμα) ISSN: 1108-2682
www.mednet.gr/eae/haema

Haema 2006; 9(0): 301-308

Carboxypeptidase G2 for Rescuing Patients with Delayed Methotrexate Elimination and Acute Renal Failure: Single Centre Experience and Literature Review

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Abstract. The experience of a paediatric oncology centre with the use of intravenous carboxypeptidase G2 (CPDG2) at doses ranging from 21 to 50U/kg for rescuing one patient with osteosarcoma and two with acute lymphoblastic leukaemia who demonstrated delayed methotrexate (MTX) elimination and acute renal dysfunction is described. The first patient developed life-threatening toxicity due to premature discontinuation of leucovorin (LV), 8 days after therapy begun. He recovered fully after the reinstitution of LV 22 days after the administration of MTX. The two others received CPDG2 92 and 69 hours after the administration of MTX along with adequate LV and recovered with no substantial toxicity. In all three patients the renal function recovered and the two patients with leukaemia were successfully retreated with 1g/m2 intravenous MTX. CPDG2 is safe and effective in rescuing patients with delayed MTX elimination and acute renal failure by decreasing the plasma MTX concentrations to non-toxic levels. Two important issues are the need for adequate LV rescue and the requirement for application of chromatographic techniques for accurately determining the serum MTX concentration post-CPDG2, since the commonly applied antibody-based assays can not reliably distinguish the parent drug from the enzymatically produced 4-amino-4-deoxy-N10-methylpteroic acid. If chromatographic techniques are unavailable, LV rescue should be continued until the serum MTX concentration is <0.05-0.1μM by antibody-based assays.

Key Words: Acute lymphoblastic leukemia • carboxypeptidase G_2 • methotrexate • osteosarcoma • renal failure • toxicity

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INTRODUCTION

Most chemotherapy protocols for osteosarcoma continue to incorporate intravenous (IV) methotrexate (MTX) in high doses, usually at 12 g/m^2/week, administered as a 4-hour infusion on two consecutive weeks along with leucovorin (LV) rescue, despite the fact that there is no consensus opinion regarding additional efficacy over doxorubicin and cisplatin alone[1-4]. Additionally, most modern chemotherapy protocols for the treatment of acute lymphoblastic leukaemia (ALL) apply high-dose methotrexate (HDMTX), i.e., doses ≥ 1g/m^2 IV, usually as a 24-hour infusion, although HDMTX has not been conclusively proven to be more effective than less toxic, labour intensive and costly

Received: , *; Accepted:* ,

Regarding $CPDG_2$'s toxicity, based on data provided by the manufacturer, among 222 patients who received the enzyme 6 developed allergic reactions, and one each headache (grade 1), fever (>39°C), grade 2 elevation of transaminases and hypertension (N. Xenodochidou, VI Pharma, Athens, Greece, personal communication). Hence, $CPDG_2$ appears safe, although anaphylactic reactions can theoretically occur since it is a bacterial protein.

In the multicentre trials, $CPDG_2$ was administered a median of 67 and 52 hours, respectively, after the start of HDMTX[32,34]. Hence, the administration of $CPDG_2$ in two of our patients (patients 1 and 3) was timely and even patient 2 received the drug <96 hours after the start of HDMTX[33].

As recommended by the manufacturer and supported by experimental data, no LV was administered for two hours before and after the administration of $CPDG_2$ due to concerns of decreased efficacy, since $CPDG_2$ could hydrolyze LV and its active metabolite 5-methyl-tetrahydrofolate, albeit with a much lower affinity compared to MTX[36]. In all three cases as depicted in Figures 1 and 2, a rebound in the serum MTX concentrations was noted around the 4^{th} to 5^{th} day after the enzyme's administration probably as a result of hydrolysis of the intracellular MTX polyglutamates by the lysosomal enzyme γ-glutamyl hydrolase[37].

Regarding the cause of delayed MTX elimination in the three patients, we can only speculate; since none of them had fluid accumulation in a third space[38] or laboratory evidence of pre-existent renal dysfunction. Moreover, none was receiving non-steroidal anti-inflammatory or other drugs associated with increased toxicity when coadministered with MTX[39,40]. Regarding the first patient, his renal function was likely compromised by the prior exposure to high doses of cisplatin, despite the normal serum creatinine. More specifically, he had received cisplatin 600mg/m^2, i.e., 120mg/m^2 more than what POG 9351 dictates[10]. Patients exposed to >300mg/m^2 cisplatin are particularly likely to have delayed MTX clearance, even with pre-treatment creatinine in the normal range[41], as was the case, since the estimated GFR prior to MTX based on various formulas[42-44] was normal. The administration of additional cisplatin in our patient was a deliberate decision, because the dose intensity of his therapy was low due to poor compliance. Regarding the delayed MTX elimination in the 20-year-old patient with ALL, older adolescents and young adults are likely at higher risk for MTX toxicity compared to children, as renal function diminishes with aging. Later on, this patient tolerated 1g/m^2 IV MTX without problems. Finally, we have no explanation for the delayed MTX elimination in the 9-year-old girl with ALL, especially since the 24-hour serum MTX concentration was not predictive of delayed MTX elimination and all recorded urine samples had urine pH in the 7-7.5 range. The only risk factors for delayed MTX elimination in this patient were the increased emesis she experienced necessitating the use of antiemetics during the 24-hour MTX infusion and the concurrent intrathecal chemotherapy with MTX[8].

As it turned out, the initial discontinuation of LV was premature in patient 1, i.e., it occurred when cytotoxic concentrations of MTX existed in the plasma. Fortunately, when 22 days after $CPDG_2$'s administration it became clear that MTX was still present due to excessive clinical toxicity, LV was restarted leading to the patient's full recovery. Unfortunately, we do not have the ability to determine plasma MTX concentrations with chromatographic techniques, such as high performance liquid chromatography (HPLC) or capillary electrophoresis. These techniques are reliable post-$CPDG_2$ administration since they can discriminate the parent drug from the enzymatically produced DAMPA[45-47]. HPLC and capillary electrophoresis are superior to the DHFR inhibition assay and especially the antibody-based techniques of MTX determination, such as the EMIT (enzyme multiplied immunoassay, Behring Diagnostics, San Jose, CA) and the FPIA, which substantially overestimate the MTX plasma concentrations post-$CPDG_2$. The overestimation of the serum MTX concentration with FPIA2 compared to the DHFR inhibition assay is clearly shown in Figure 1.

Our report is also instructive of the importance of supportive care after $CPDG_2$ for MTX-induced renal dysfunction, since patient 1 survived 31 days of grade 4 complicated neutropenia.

In conclusion, the timely administration of $CPDG_2$ is effective in patients with delayed MTX elimination and renal dysfunction. However, it is extremely important for effective post-enzyme rescue to continue the administration of adequate LV and to maintain alkaline urine. In cases that chromatographic techniques for measuring the MTX concentration post-$CPDG_2$ are unavailable, LV should be continued until the renal function has recovered and the serum MTX is < 0.05-0.1μM by antibody-based assays. Finally, all oncology centers using HDMTX should have an established emergency protocol for administration of $CPDG_2$.

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